Exhibit A

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Letter to the Editor

The citation and abstract of the article discussed below is as follows:

Activated Protein C Differs from Protein C Pharmacokinetically and Pharmacodynamically

To the Editor: The report by Roback et al. demonstrating improved survival after treatment with human activated Protein C (hAPC) as compared with placebo in rabbits challenged with meningococcal endotoxin is very interesting. However, the authors indiscriminately and incorrectly used the two terms "activated Protein C" and "Protein C" throughout the paper and thus made the Introduction and Discussion sections very confusing. As a result, the authors failed to discuss a very important point in their paper. In view of the recent optimism generated by several open-label studies which treated meningococcemia patients presenting with purpura fulminans with Protein C concentrate, Roback et al. failed to discuss why they only tested activated Protein C and not also Protein C in their meningococcal endotoxin-challenged rabbit model.

Protein C differs from activated Protein C both pharmacokinetically and pharmacodynamically. Protein C is a vitamin K-dependent protein and circulates as an inactive zymogen in humans at about 4 μg/ml. Protein C is converted to the active serine protease, activated Protein C, by thrombin in complex with an endothelial membrane protein, thrombomodulin. Activated Protein C circulates at a much lower concentration of about 2 ng/ml in humans. Protein C has a half-life of about 10 h in humans. Activated Protein C has a half-life in humans of about 23–45 min, more than 10 fold shorter than the zymogen, Protein C. Activated Protein C prolongs aPTT clotting time in treated subjects while Protein C, the zymogen, does not. Thus Protein C and activated Protein C are two very different molecules and care must be taken to avoid interchanging the nonclinical and clinical experience with these two molecules.

Thus far in the published literature, including the study by Roback et al., only activated Protein C, and not Protein C, has been tested and shown to be efficacious in nonclinical sepsis models. The nonclinical baboon bacteremic sepsis study conducted by Taylor et al., as cited by Roback et al. (1), tested activated Protein C and not Protein C. The wrong molecule was cited by the authors in the Introduction and Discussion sections. In contrast to the published nonclinical pharmacology data, the published clinical experience in treating either congenital homozygous Protein C deficiency or meningococcemia patients presenting with purpura fulminans has all been with Protein C the zymogen, not activated Protein C. Again, the wrong molecule was cited by the authors in the Introduction and Discussion sections. To date so far, all the nonclinical experience in sepsis models has been with activated Protein C and the clinical experience with Protein C. Is Protein C as effective as activated Protein C in the treatment of severe sepsis? Is there an advantage of one molecule over the other in the treatment of severe sepsis? There is a very important missing link as yet to be answered between the nonclinical and clinical experience of these two molecules, activated Protein C and Protein C in the treatment of severe sepsis.

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